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# Physicians' Preferences for Bone Metastases Drug Therapy in the United States

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ABSTRACT

**Objective:** Several characteristics of bone-targeted agents are considered when making treatment decisions. This study evaluated physicians' therapy preferences for preventing skeletal-related events (SREs) in patients with bone metastases secondary to solid tumors. **Methods:** A Web-enabled, discrete-choice experiment online survey was conducted among physicians who treated patients with bone metastases and solid tumors in the United States. Respondents chose between pairs of hypothetical medications defined by combinations of six attributes at varying levels for two hypothetical patients. Preference weights for attribute levels were estimated using a random-parameters logit model. **Results:** In total, 200 physicians completed the survey. Their mean age was 52 years, 57% were in practice for more than 15 years, 37% were oncologists, and 65% treated 10 or fewer patients with bone metastases weekly. Out-of-pocket cost to patients was the most important attribute overall. Among clinical outcomes, time to first SRE and risk of renal impairment were the most important attributes. Statistically significant preferences were observed for all attribute levels for time to first SRE, risk of renal impairment, and mode of administration. Predicted choice probability analysis showed that physicians preferred a hypothetical medication with attributes similar to those of denosumab over one with attributes similar to those of zoledronic acid. **Conclusions:** Physicians indicated that clinical attributes are important when considering bone-targeting therapy for bone metastases, but consistent with the current health care landscape, patient out-of-pocket cost was the most important. With health care costs being increasingly shifted to patients, physicians require accurate information about co-pays and assistance programs to avoid patients receiving less costly, yet potentially inferior, treatment.

*Keywords:* bone metastases, conjoint analysis, discrete-choice experiment, drug therapy attributes, preferences, skeletal-related events, treatment.



## Introduction

Bone is the most common site for metastasis in cancer, especially in breast and prostate cancers [1]. Approximately 70% of patients with metastatic breast or prostate cancer will develop bone metastases [1–4]. Bone metastases are also common in patients with advanced lung, kidney, or thyroid cancer, with an estimated incidence of 30% to 40% observed postmortem [1,5,6]. The prevalence of metastatic bone disease across all cancer types in the US adult population is estimated to be 280,000 cases, although this number is likely an underestimate because of underdiagnosis and underreporting of cases in claims data [7].

*Skeletal-related events* (SREs), defined as pathologic fractures, spinal cord compression, and surgery or radiation to bone, are serious skeletal complications that occur frequently in patients with bone metastases [2,8]. Although the term SRE refers to a combination of spontaneous medical events (spinal cord compression or pathologic fracture) or a clinically significant unplanned medical procedure (radiation to bone or surgery to bone) that is initiated in response to severe pain or imminent/actual pathologic fracture, both are associated with significant humanistic and economic burden to the patient and the health care system. SREs are debilitating and may lead to pain and impaired mobility, and thus, reduced health-related quality of life, as well as increased mortality [1,6]. Health care costs associated with SREs are considerable [9–11], with average medical costs of $54,751 and $11,768 (2010 US dollars) for managing each inpatient and outpatient SRE episode, respectively [12].

Conflicts of interest: A. Brett Hauber and Juan Marcos Gonzalez are employees of RTI Health Solutions, an independent scientific research organization. The study that is the subject of this article was conducted by RTI Health Solutions and funded by Amgen. Ateesha F. Mohamed was employed by RTI Health Solutions at the time of development of this article. Jorge Arellano, Guy Hechmati, Francesca Gatta, and Yi Qian are employees of Amgen. Helen Collins was employed by Amgen at the time the study was conducted.

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Before the availability of denosumab, drug therapy options for bone metastasis in the United States were limited to bisphosphonates, predominantly zoledronic acid. In 2010, denosumab was approved by the US Food and Drug Administration for the prevention of SREs in patients with bone metastases associated with solid tumors on the basis of its superiority to zoledronic acid in delaying the first onset of SREs (median 8.21 months) in three randomized controlled trials [13]. Nonetheless, treatment decisions may not solely depend on the efficacy profile of a drug therapy; factors such as the safety profile (e.g., adverse events), mode of drug administration (e.g., intravenous vs. subcutaneous route), and out-of-pocket costs to patients may also play an important role. In addition to the superior efficacy of denosumab over zoledronic acid, the attributes that may influence decisions are different between the two options [14–17].

Physician preferences for pharmacologic therapy to prevent or delay SREs in cancer patients with bone metastases have not been assessed. The primary objective of this study was to assess and quantify these preferences in the US setting.

To achieve this, we used a discrete-choice experiment (DCE) to assess the medication preferences of physicians in the United States. DCEs have increasingly been used in medicine [18,19] and are grounded in both psychology [20] and economics [21]. DCEs offer a systematic method of eliciting trade-offs to quantify the relative importance physicians, other health care decision makers, or patients place on various treatment characteristics or treatment-related outcomes [19]. This approach is based on the premise that treatments comprise a set of outcomes or treatment features or attributes (e.g., efficacy, adverse events, and mode of administration) and that the relative value of a treatment to an individual is a function of these attributes. The investigators in this study followed best practices [22] in designing and administering a DCE (also known as a choice-format conjoint-analysis survey) to elicit physician preferences for a pharmacologic therapy for the prevention of SREs in patients with bone metastases secondary to a solid tumor.

## Methods

### Survey Instrument

Six attributes of currently available medications for the prevention of SREs in patients with bone metastases were identified for evaluation and were based on the US product label information, scientific literature, clinical trial results, and consultation with clinical experts (Table 1) [14,15,23]. *SRE* was defined as skeletal complications including pathologic fracture, radiation or surgery to bone, or spinal cord compression. *The risk of osteonecrosis of the jaw* was defined as the annual risk for developing an exposed area of the jawbone for at least 8 weeks. *The risk of renal impairment* was defined as the annual risk of a 0.5-mg/dL increase in baseline serum creatinine level. Attribute levels were designed to encompass the ranges commonly observed in current clinical practices as well as the ranges over which physicians are willing to accept trade-offs among attributes. The levels for the cost attribute were determined to span the range of likely out-of-pocket costs that patients in the United States might incur. Survey validation included open-ended interviews with eight physicians in Philadelphia, PA. These interviews were conducted (either in person or by phone) to 1) test the clarity of the survey instrument and the appropriateness of the descriptive information; 2) confirm that the six attributes included in the survey were salient to physicians; 3) confirm that no other salient attributes were missing; and 4) assess physicians' willingness to accept trade-offs among attributes in evaluating hypothetical drug therapies. The attributes for the survey questions were presented in an order that reflected the product labeling and the order in which a physician might normally communicate to patients.

**Table 1 – Attributes and levels for the choice questions.**

| Attribute | Levels |
|---|---|
| Time until first SRE | 28 mo |
| | 18 mo |
| | 10 mo |
| Time until a 2-point increase in pain on the BPI-SF (time until worsening of pain) | 10 mo |
| | 6 mo |
| | 3 mo |
| Risk of ONJ each year | None |
| | 1 out of 100 (1%) |
| | 5 out of 100 (5%) |
| Risk of 0.5-mg/dL increase in baseline creatinine each year (risk of renal impairment) | None |
| | 4 out of 100 (4%) |
| | 10 out of 100 (10%) |
| Mode of administration and frequency | Injection every 4 wk |
| | 15-min infusion every 4 wk |
| | 120-min infusion every 4 wk |
| Out-of-pocket cost to the patient each month ($) | 25 |
| | 75 |
| | 150 |
| | 330 |

BPI-SF, Brief Pain Inventory Short Form; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.

To create drug therapy profile pairs for the choice questions, an established algorithm was used to construct a main-effects experimental design maximizing D-efficiency using SAS (version 9.3; Cary, NC). The final design included four survey versions, each with 9 choice questions (36 choice questions in total), with the order of the questions randomized within survey versions. One of the questions shown was repeated as the third, seventh, eighth, or ninth choice question. Respondents answered 10 choice questions between pairs of hypothetical drug profiles (Fig. 1), making prescribing decisions in each question for one of two hypothetical patient profiles (Table 2). Respondents were randomly assigned to one of four survey versions.

### Patient Profiles

Patient profiles were based on one of two hypothetical profiles (Table 2). These profiles were evaluated during the pretest phase with physicians, who reported that the profiles were representative of patients in their practices. Physicians saw both profiles at the beginning of the survey. Profiles 1 and 2 were presented in odd- (1, 3, 5, 7) and even-numbered (2, 4, 6, 8) questions, with the full profiles presented in questions 1 and 2 and an abridged version presented for questions 3, 5, and 7 and 4, 6, and 8, respectively. In questions presenting the abridged version of the patient profile, the respondent could click on a hyperlink to reveal the full description of the patient.

### Study Sample

Practicing, board-certified physicians who were currently involved in treating patients with bone metastases from a solid tumor were eligible. A survey research company recruited members from existing online physician panels and administered the

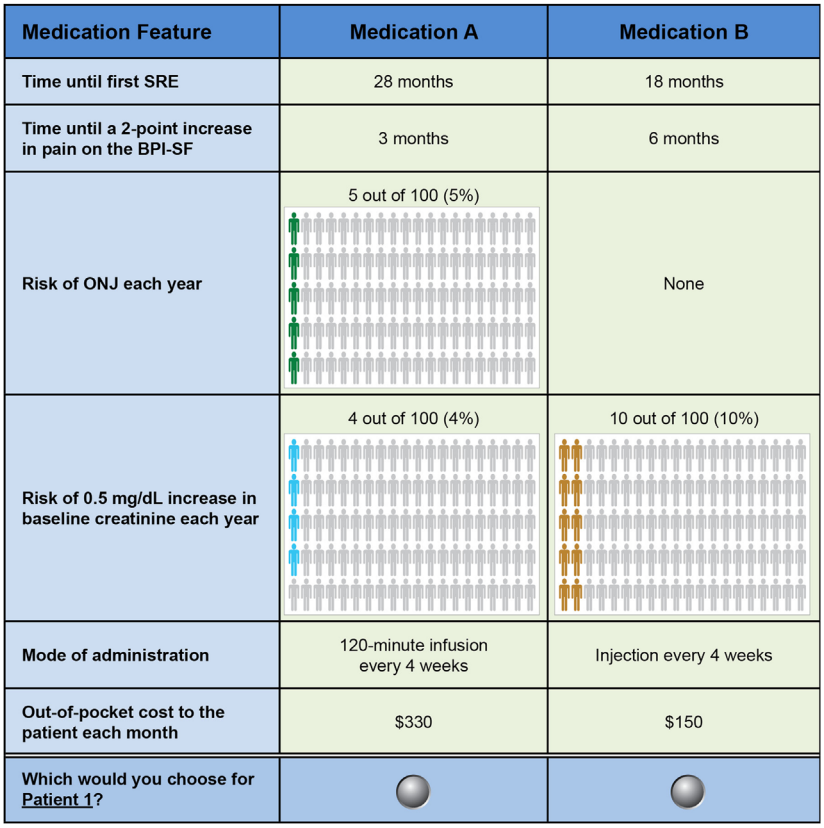


**Fig. 1 – Example of choice questions. BPI-SF, Brief Pain Inventory Short Form; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.**

25-minute survey in January and February 2013. Ethical considerations were reviewed by the Office of Research Protection and Ethics at the responsible study organization (RTI International; Research Triangle Park, NC). Upon recruitment, physician respondents provided online informed consent. Demographic information for the respondents was collected. Respondents were excluded if there was no variation in responses to choice questions (i.e., responder chose the same option for all 10 questions) because this was considered to indicate lack of attention to the questions.

### *Statistical Analysis*

Descriptive statistics, including respondents' demographic characteristics and clinical experiences, were reported. A random-parameters logit model [24,25] was used to analyze the pattern of physicians' choices. Such a model relates the selection of a profile to differences in attribute levels between hypothetical treatment alternatives. The model results reflect the effect of attribute levels on the likelihood that a treatment is selected. Thus, random-parameters logit estimates are considered mean preference weights for attribute levels. Each preference weight indicates the relative strength of preference for an attribute level—more preferred outcomes have higher preference weights.

All attribute levels were modeled as categorical variables using effects coding [24,25]. The 95% confidence intervals of the estimates were calculated for each preference weight. Statistically significant differences between weights for attribute levels were tested using a Wald test. Differences in preference-weight estimates for levels in an attribute indicate the importance of changing a treatment attribute from one level to the other. The difference between the most and least important levels of an attribute indicates the overall relative importance of the range of levels in the attribute. Estimated preference weights were also used to calculate predicted choice probabilities for drug therapy profiles. Predicted choice probabilities were calculated by adding the preference weights for the attribute levels in each of several available treatments to determine the proportion of physicians who would select each profile [26]. Differences in preferences for each attribute were calculated as the denosumab value times the preference weight minus the zoledronic acid value times the preference weight.

A post hoc analysis was performed to determine any differences in preferences for attribute levels between oncologists and all other specialties combined. The statistical significance of all estimated differences was jointly tested using a Wald test. All statistical analyses were conducted using NLOGIT 4.0 (Econometric Software, Inc., Plainview, NY).

## Results

### *Response Rate*

A total of 5020 US physicians were invited to participate in the survey. Of those invited, 341 individuals (7%) responded to the invitation and, of those who responded, 260 (76%) were eligible to participate (i.e., those physicians who were practicing, board-certified, and currently treating patients with bone metastases from solid tumors). A total of 256 of 260 (98%) eligible physicians consented to participate and 200 (78%) completed the survey. Data for all 200 physicians were included in the final analysis.

**Table 2 – Patient profiles.**

| Profile | Description |
|---|---|
| Patient profile 1 | A 57-y-old woman who was diagnosed with breast cancer and developed bone metastases along with 2-cm mediastinal and supraclavicular adenopathy 3 y after her initial diagnosis. She initially received TC adjuvant chemotherapy. The tumor was ER/PR positive and HER2 negative. She was on an adjuvant aromatase inhibitor at the time of her relapse. Her recurrence was noted by examination identifying the supraclavicular adenopathy. On further questioning she admits to increasing midback (thoracic area) pain, which she rates as a 4 on a scale of 0–10. The patient's health is otherwise good (high performance status) with no history of kidney disease and no significant comorbidities. |
| Patient profile 2 | A 71-y-old man who was initially diagnosed with Gleason 8-10 prostate cancer 3 y ago. He is now castration resistant and has developed bone metastases. His PSA level is ≥10. He is complaining of left hip pain when he walks and low back pain if he sits too long, which he rates as a 4 on a scale from 0 to 10. The patient's health is otherwise good (high performance status), with no history of kidney disease and no significant comorbidities. |

ER/PR, estrogen receptor/progesterone receptor; HER2, human epidermal growth receptor 2; PSA, prostate-specific antigen; TC, docetaxel/cyclophosphamide.

### *Sample Characteristics*

Demographic characteristics for the 200 respondents are presented in Table 3. The mean age of physicians in the sample was 51.9 years. Physicians were board-certified in 44 different states, with 69 (34.5%) of them certified in states in the northeastern region, 33 (16.6%) in the midwest region, 66 (33.0%) in the southern region, and 32 (16.0%) in the western region of the United States. Most (82.0%) physicians had been in practice for more than 10 years since completing their medical training, and more than half (56.5%) had been in practice for longer than 15 years. Most of the physicians (71.0%) indicated that they were in an office-based private practice. The most frequently noted areas of specialization were oncology (37.4%) and primary care (12.6%); nearly half (49.5%) of the physicians described their specialty as "other." All physicians treated patients with bone metastases from solid tumors, typically up to 10 patients each week (65.0%). The Brief Pain Inventory Short Form was used in their practice for all patients by 15.0% of the physicians and for most patients by 27.5% of the physicians.

### *Preference Weights*

The preference weights for the six attributes (time until first SRE, time until 2-point increase in pain on the Brief Pain Inventory Short Form, risk of osteonecrosis of the jaw each year, risk of 0.5-mg/dL increase in baseline creatinine level each year [risk of renal impairment], mode of administration, and out-of-pocket cost to patient each month) included in the analysis from Table 1 are presented in Figure 2. The parameter estimates can be interpreted as the relative strength of preference for each attribute level [22]. As seen in Figure 2, the most important attributes were out-of-pocket expenses, time until first SRE, and risk of renal impairment. The mean estimates were ordered as expected for time until first SRE and risk of renal impairment, with better clinical outcomes having higher estimates; the mean estimates were statistically significantly different between all adjacent levels ($P < 0.05$). Mean estimates were ordered as expected for time until worsening of pain, risk of osteonecrosis of the jaw, and out-of-pocket cost, but the first two adjacent levels were not statistically significantly different ($P > 0.05$). The mode of administration does not have a natural ordering, but an injection every 4 weeks was significantly preferred over a 15-minute infusion every 4 weeks ($P < 0.05$), and a 15-minute infusion every 4 weeks was significantly preferred over a 120-minute infusion every 4 weeks ($P < 0.05$).

For each attribute level, the difference in preferences between oncologists and all other physicians was estimated in a post hoc analysis. The null hypothesis for the test was that all estimated differences were zero. The estimated $P$ value for the Wald test was 0.2982, suggesting that there is no difference between oncologists' preferences and preferences of other physicians in the study. With respect to the hypothetical patient profiles, no statistically significant differences in physician treatment preferences were observed between responders with full access to either patient profile.

### *Predicted Choice Probabilities*

The profiles of attributes for denosumab and zoledronic acid were derived from the prescribing information and clinical trial data for these products [14,15,23] and are summarized in Table 4. Data for the predicted choice probabilities in terms of the percentages that one alternative with its associated attributes would be chosen over the other are also presented in Table 4. Physicians were not directly asked about their preference for existing

**Table 3 – Demographic characteristics for respondents.**

| Category | Physicians (N = 200) |
|---|---|
| Age (y), mean ± SD | 51.9 (10.4) |
| No. of years in practice (%) | |
| 1–9 | **36 (18)** |
| 10–20 | **88 (44)** |
| >20 | 76 (38) |
| Type of practice, n (%) | |
| Office-based private practice | 142 (71.0) |
| Hospital-based private practice | 30 (15.0) |
| Academic hospital-based practice | 44 (22.0) |
| Other | 3 (1.5) |
| Area of specialty, n (%) | |
| Primary care | 25 (12.6) |
| Family medicine | 1 (0.5) |
| Oncology | 74 (37.4) |
| Other | 98 (49.5) |
| Missing | 2 (1) |
| No. of patients with bone metastases from solid tumors treated each week (%) | |
| ≤5 | 78 (39) |
| 6–10 | 52 (26) |
| >10 | 70 (35) |
| Use of the BPI-SF to assess pain level in patients with bone metastases, n (%) | |
| All patients | 30 (15.0) |
| Most patients | 55 (27.5) |
| A few patients | 33 (16.5) |
| Do not use | 82 (41.0) |

BPI-SF, Brief Pain Inventory Short Form.

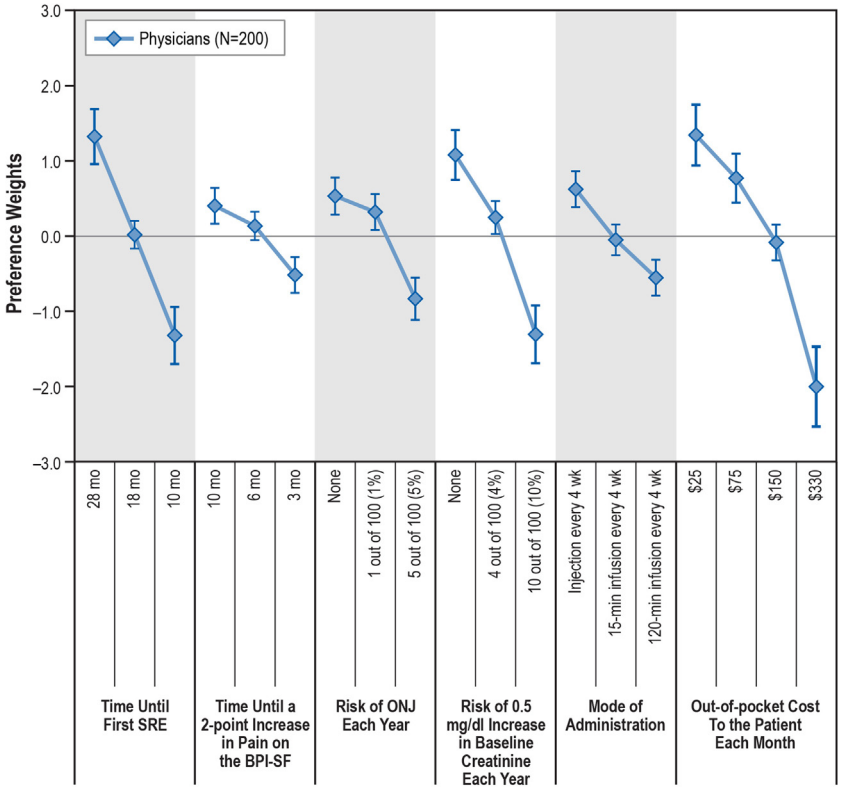


**Fig 2 – Preference-weight graph. The vertical bars surrounding each mean preference weight denote the 95% CI about the point estimate. If the CIs do not overlap for adjacent levels in a particular attribute, the mean estimates are statistically different from each other at the 5% level of significance. BPI-SF, Brief Pain Inventory Short Form; CI, confidence interval; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.**

treatments, but on the basis of preference estimates from the survey results, physicians preferred a drug therapy with attributes similar to those of denosumab (98.4%; 95% confidence interval, 95.6%–99.5%) over a drug therapy with attributes similar to those of zoledronic acid (1.6%; 95% confidence interval, 0.6%–4.4%). The major clinical contributors influencing the choice between the two drugs were risk of renal impairment and the occurrence of SREs. This is observed by the difference in preference between denosumab and zoledronic acid for each attribute (Table 4), which was 2.20 for renal impairment (favoring denosumab) and 1.05 for time until first SRE (favoring denosumab).

## Discussion

The results of this DCE analysis showed that given the range of levels included, physicians consider out-of-pockets costs to patients, time until the first SRE, and risk of renal impairment

**Table 4 – Predicted Choice Probabilities.**

| Attribute | Characteristics Similar to Denosumab | Characteristics Similar to Zoledronic Acid | Preference Difference (Denosumab–Zoledronic Acid) |
|---|---|---|---|
| Profiles* | | | |
| Time until first SRE, mo | 27.7 | 19.5 | 1.05 |
| Time until worsening of pain, mo | 6.6 | 4.7 | 0.32 |
| Risk of ONJ, % | 1.8 | 1.3 | –0.14 |
| Risk of renal impairment, % | 0 | 9.3 | 2.20 |
| Mode of administration | Injection every 4 weeks | 15-min infusion every 4 weeks | 0.68 |
| Predicted choice probabilities† | 98.4% (95.6%–99.5%) | 1.6% (0.6%–4.4%) | NA |

NA, not applicable; ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.

* Values derived from prescribing information for denosumab[14] and zoledronic acid [15].

† Values represent the predicted probability (95% CI) that each alternative with its associated attributes would be chosen if these profiles represented the only available treatment options.

as the most important attributes when choosing pharmacologic therapy for the prevention of SREs in patients with bone metastases due to solid tumors. Given that out-of-pocket costs are the most important attribute in this analysis, it seems that physicians understand that such costs, which vary in the United States by health plan and coverage, are an important factor for patients, and indeed, studies have confirmed that this is of relatively equal importance for both physicians and patients [27]. These observations underscore the importance of increasing awareness of health plan coverage and patient support programs to enable caregivers to present a more comprehensive view of available treatment options for bone metastases, facilitating a joint treatment decision between physicians and patients.

The predicted choice probabilities derived from these results demonstrated that physicians preferred a hypothetical pharmacologic therapy with attributes similar to those of denosumab over a hypothetical pharmacologic therapy with attributes similar to those of zoledronic acid. This study was specifically designed to isolate preferences for therapeutic choices from perceptions based on marketing and preconceptions of currently available therapies.

A number of study limitations need to be considered. Respondents were asked to make simulated clinical decisions on hypothetical drug therapies, which have hypothetical rather than actual consequences. We have attempted to minimize this bias by making the hypothetical choices mimic real-world tradeoffs as closely as possible and by verifying the survey attributes with open-ended interviews during survey testing. The response rate for this study was low (<10%), and data on the characteristics of nonrespondents are not known (i.e., those who did not meet the inclusion criteria or who did not consent to participate). Thus, the recruitment procedure used in this study may have resulted in selection bias. In addition, only 37% of the respondents were oncologists, who are most likely to manage patient treatment for bone metastases from solid tumors, and nearly 50% of the respondents indicated "other" as their specialty. A post hoc analysis, however, showed that results were similar for oncologists versus nononcologists (all the remaining physicians in the study), although the study was not designed to detect the difference between subgroups of respondents. Payment by the health care insurer was not included as a question because the purpose of the study was to evaluate the preference for a medication on the basis of attributes that directly affect the patient. Moreover, this study did not investigate whether physicians have reliable tools to determine out-of-pocket costs for an individual patient.

To our knowledge, this is the first discrete-choice study to evaluate physicians' preferences for drug therapies for bone metastases secondary to solid tumors. Bone-targeted therapy is needed in patients with bone metastases to delay or prevent SREs and to maintain or improve patients' quality of life. Determining physicians' preferences for pharmacologic therapy helps understand their decision-making process when considering multiple treatment options and highlights the physicians' priorities regarding the treatment attributes. This, in turn, should aid other physicians' decisions about patient management and, in this situation, improve the management of bone metastases when available alternatives exist.

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